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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/723,431
Filing Date: November 26, 2003
Appellant(s): HU ET AL.

John W. Mickelson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 2-16-10 appealing from the Office action mailed 1-12-09.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application: 1-28, 30-31, 33, 40-42 and 47-71.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

WO 99/13816	MOYNIHAN	3-1999
US 2003/0124181	TARDI	7-2003
5,814,335	WEBB	9-1998
5,939,096	CLERC	8-1999

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 1-28, 30-31, 33, 40-42 and 47-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 in combination with Tardi (US 2003/0124181).

WO 99 discloses a method of loading camptothecins using a pH gradient at a higher temperature, which is same as instant method. The lipids used include DSPC, cholesterol and phosphatidylglycerols. The buffer used is citrate buffer which is more than 5 mM. The lipid to camptothecin ratios are from 5:1 to 100:1 (abstract, pages 10-15, 18, Example 2 and claims). Although in examples, WO uses citric acid at 50 mM concentration, in view of WO's teachings that it can be higher than 5 mM, it would have been obvious to one of ordinary skill in the art to vary the molarity with the expectation of obtaining the best possible results. What is lacking in WO is the loading of active agents other than camptothecins, such as claimed anthracyclines and vinca alkaloids.

Tardi while disclosing liposomal compositions containing various active agents teaches that therapeutic agents which can be loaded using pH gradients comprise one more ionizable moiety such that the neutral form of the ionizable moiety allows the drug to cross the liposome membrane and conversion of the moiety to charged form causes the drug to remain encapsulated within the liposomes. Tardi teaches that the ionizable moieties comprise amine, carboxylic acid and hydroxyl groups. Among the active agents taught by Tardi are camptothecins, vinca alkaloids such as vinblastine, and vincristine and anthracycline antibiotics such as doxorubicin (0080-0081). Tardi further teaches dehydrating the liposomes and the use of cryoprotectants (claims).

The use of the liposomes of WO to load active agents such as anthracycline antibiotics and vinca alkaloids would have been obvious to one of ordinary skill in the art

since Tardi teaches that any ionizable active agent having an amine, carboxyl and hydroxyl functional groups can be loaded using pH gradients and those compounds include camptothecins, anthracyclines and vinca alkaloids.

WO does not teach the use of sphingomyelin in the preparation of the liposomes, since it is a commonly used lipid in the liposome formations, it would have been obvious to one of ordinary skill in the art to use this lipid with a reasonable expectation of success.

2. Claims 7 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 in combination with Tardi as set forth above, further in view of Webb (5,814,335) of record.

The teachings of WO and Tardi have been discussed above. What is lacking in these references is the use of sphingomyelin as the liposome-forming lipid. The use of sphingomyelin however, would have been obvious to one of ordinary skill in the art since Webb teaches that sphingomyelin containing liposomes are stable and have extended circulation time (abstract). Neither EP nor WO teaches the change of the pH of the external medium by using methylamine. The use of methylamine to change the pH of the external medium would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Webb teaches the creation of pH gradient using methylamine (columns 7 and 8).

3. Claims 52-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/13816 in combination with Tardi (US 2003/0124181) as set forth above, further in view of Clerc (5,939,096).

The teachings of Tardi and WO have been discussed above.

Clerc while disclosing a method of drug loading by pH gradient teaches that liposomes can be dehydrated for storage in the presence of cryoprotectant sugars (col. 8, lines 9-15). It would have been obvious to one of ordinary skill in the art to use cryoprotectants and dehydrate liposomes since they can be stored in that state as taught by Clerc.

4. Claims 1-28, 30-31, 33, 40-42 and 47-71are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-31 and 35-64 of U.S. Patent No. 6,740,335 in combination with Tardi (US 2003/0124181). Although the conflicting claims are not identical, they are not patentably distinct from each other because both patented claims and instant claims are drawn to the process of loading agents using pH gradients. Instant claims are generic with respect to the active agents loaded whereas the patented claims recite specific camptothecin compound. However, it would have been obvious to one of ordinary skill in the art to load any active agent using a pH gradient with a reasonable expectation of success since Tardi teaches that any ionizable active agent having an amine, carboxyl and hydroxyl functional groups can be loaded using pH gradients and those compounds include camptothecins, anthracyclines and vinca alkaloids. Patented claims do not

recite the concentration of the acid while loading the active agent and instant mM amounts therefore, are deemed to be anticipated by the claims in the patent.

(10) Response to Argument

REJECTION 1:

Appellant's arguments have been fully considered, but are not persuasive. Appellant mainly focuses on Tardi's teachings and argues that Tardi primarily focuses on the preparation of liposomes from negatively charged lipids that are stable in the blood and at paragraphs 0072-0083, according to appellant although Tardi does generally discuss both the passive and active loading of liposomes, gradient loading is not the focal point of the Tardi invention. These arguments are not persuasive since irrespective of what focal point of Tardi's invention is, as recognized by appellant, Tardi at this location (0072-0083) clearly teaches the use of gradients (K+, Na+ and H+) for compound loading; Tardi also clearly states in 0080 that camptothecins, vinca alkaloids such as vinblastine, vincristine and novelbine and anthracycline antibiotics such as doxorubicin could be loaded using pH gradients. In essence, Tardi clearly equates camptothecins taught by WO with anthracycline antibiotics and vinca alkaloids in terms of gradient loading.

Appellant argues that Tardi does not teach the preparation of any liposomes using the quenching step. Further according to applicant, the final liposomes prepared by Tardi maintain a low pH in the internal aqueous space that helps keep the drug

loaded in the liposomes and according to appellant, Tardi teaches that it is critical to maintain the low pH in the internal aqueous space after active drug loading of the liposome in order to keep the therapeutic agent trapped inside. Further according to appellant, one skilled in the art would not have had a reasonable belief that the recited anthracyclines and vinca alkaloids generally discussed in Tardi could have been loaded using the method of WO since Tardi teaches that the low pH in the interior of the liposome is critical for keeping the agent inside the liposome following gradient loading and therefore Tardi teaches away. These arguments are not persuasive and the examiner disagrees with appellant's interpretation that the low pH in the interior of liposomes in Tardi is critical since Tardi at this location only teaches the principles of drug loading using gradients and as appellant himself states that pH loading is not the focus of Tardi. In essence, Tardi is combined for its teachings of equating the camptothecins of WO with claimed anthracyclines and vinca alkaloids as ionizable drugs and which can be loaded using gradients which is also the focus of WO. According to the teachings of WO on page 14, lines 16-22 the drug loading by pH gradient usually includes low pH in the internal aqueous space of the liposomes and this acidity is incompletely neutralized during the drug loading process. Further according to WO, this residual internal acidity can cause chemical instability in the liposomal preparation (e.g. lipid hydrolysis) leading to limitations in shelf life. Therefore, WO advocates quenching this residual internal acidity using membrane permeable amines such as ammonium salts or alkyl-amines. It is the examiner's position that the lipid hydrolysis would remain the same irrespective of the loaded drug one of ordinary skill in

the art would be motivated to quench the internal pH using a weak base even when loading anthracyclines or vinca alkaloids.

As pointed out before, Tardi is combined since WO does not teach drugs other than camptothecins and Tardi teaches the equivalency between camptothecins and claimed anthracyclines and vinca alkaloids. Since all of them are ionizable compounds, one of ordinary skill in the art would be motivated to use the method of WO to load even anthracyclines and vinca alkaloids. Applicant has not shown any unexpected results by using the method taught by WO for loading these drugs.

Appellant disagrees with the examiner's position that although in Examples WO uses citric acid at 50 mM concentration in view of WO's teachings that it can be higher than 5 mM and therefore it would have been obvious to one of ordinary skill in the art to vary the molarity with the expectation of obtaining the best possible results and argues that one skilled in the art would have believed that gradient loading using a high concentration of citric acid would produce a final liposome with a higher concentration of therapeutic agent in the liposome than would be produced by gradient loading a lower concentration of citric acid and therefore one skilled in the art would have known that gradient loading using a higher concentration of acid would produce a final liposome that is potentially less thermodynamically stable, i.e., a liposome wherein the therapeutic agent is more likely to leak or escape from the liposome. This argument is not persuasive since appellant's statement appears to be speculative since it is not accompanied by any evidence why one skilled in the art would expect that way. The examiner also points out that since more ionizable therapeutic agent is there along with

higher amounts of citric acid, one would expect the therapeutic agent to be in a neutral state. In addition, the examiner points out that WO teaches the quenching of the excess acid with a base. The examiner also points out that instant claims do not recite any specific amounts of therapeutic agent and therefore, arguments that higher concentration of concentration is utilized in the loading process and when a higher concentration of citric acid is utilized during a gradient loading process, the amount of therapeutic agent present in the final liposomes is not great enough to neutralize a majority of the residual acid are not persuasive. Finally it should be pointed out that instant lower limit is 60 mM and WO in examples teaches 50 mM and applicant has not shown any unexpected results obtained by this change in the concentration.

In response to the examiner's position that the use of sphingomyelin would have been obvious to one of ordinary skill in the art since it is a known liposome forming lipid, the appellant argues that the examiner has provided no evidence to support this line of reasoning. The examiner disagrees and points out the reference of Webb which is discussed below supports the examiner's position.

Appellant argues that claim 42 is dependent on claim 1 and recites "wherein the solution is cooled in step (c) to a temperature of about 0^0 C to about 30^0 C and the office fails to establish a prima facie case of obviousness with respect to claim 42 and according to appellant the primary reference does not teach this limitation. Appellant is incorrect in this statement since in Example 2 (page 21, lines 22-24), WO teaches cooling to ***below 35 ^{0} C.***

Appellant's arguments that the inclusion of claim 49 is an error are not persuasive since the prior art clearly indicates that methylamine is a commonly used base in liposome technology. The examiner also points out to WO's teachings on page 14, lines 19-22 that quenching can be performed by ammonium salts or alkyl amines. Methylamine is an alkyl amine (see also claims 50 and 53 which recite methylamine). Applicant's arguments that the inclusion of claims 52-57 is an error are not persuasive since Tardi clearly shows the use of cryoprotectants (claims).

Appellant's arguments regarding claim 63 are not persuasive since mere addition of a pharmaceutically acceptable carrier to the loaded liposomes of claim 1 does not make the claim patentable since it is within the skill of the art to add appropriate carriers.

Appellant's arguments with regard to claim 71 are not persuasive for the same reasons above since this claim is a product claim prepared by the process taught by WO.

REJECTION 2:

Appellant's arguments have been fully considered, but are not persuasive. The examiner has already addressed appellant's arguments regarding WO and Tardi. Appellant provides no specific arguments regarding the use of sphingomyelin taught by Webb. Appellant argues that Webb uses methylamine for a significantly different function. This argument is not persuasive since methylamine is a base which is commonly used for changing the pH while loading drugs into the liposomes and it is

within the skill of the art to use any base including methylamine with the expectation of obtaining similar pH changes and appellant has not shown any unexpected results by using methylamine. Furthermore, as already pointed out, WO teaches quenching by methylamine.

REJECTION 3:

Appellant's arguments have been fully considered, but are not persuasive. The examiner has already addressed appellant's arguments regarding WO and Tardi. Appellant provides no specific arguments regarding the use of cryoprotectants taught by Clerc.

REJECTION 4:

Appellant's arguments have been fully considered, but are not persuasive. The essence of appellant's arguments is that WO 99/13816 is a counter part of US 6,740,335 and therefore, the same arguments as above are applicable. The examiner has already addressed those arguments. The rejection therefore, is maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Gollamudi S Kishore/

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